GluR5 Kainate Receptors, Seizures, and the Amygdala

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ABSTRACT: The amygdala is a critical brain region for limbic seizure activity, but the mechanisms underlying its epileptic susceptibility are obscure. Several lines of evidence implicate GluR5 (GLU_{K5}) kainate receptors, a type of ionotropic glutamate receptor, in the amygdala's vulnerability to seizures and epileptogenesis. GluR5 mRNA is abundant in temporal lobe structures including the amygdala. Brain slice recordings indicate that GluR5 kainate receptors mediate a portion of the synaptic excitation of neurons in the rat basolateral amygdala. Whole-cell voltage-clamp studies demonstrate that GluR5 kainate receptor-mediated synaptic currents are inwardly rectifying and are likely to be calcium permeable. Prolonged activation of basolateral amygdala GluR5 kainate receptors results in enduring synaptic facilitation through a calcium-dependent process. The selective GluR5 kainate receptor agonist ATPA induces spontaneous epileptiform bursting that is sensitive to the GluR5 kainate receptor antagonist LY293558. Intra-amygdala infusion of ATPA in the rat induces limbic status epilepticus; in some animals, recurrent spontaneous seizures occur for months after the ATPA treatment. Together, these observations indicate that GluR5 kainate receptors have a unique role in triggering epileptiform activity in the amygdala and could participate in long-term plasticity mechanisms that underlie some forms of epileptogenesis. Accordingly, GluR5 kainate receptors represent a potential target for antiepileptic and antiepileptogenic drug treatments. Most antiepileptic drugs do not act through effects on glutamate receptors. However, topiramate at low concentrations causes slow inhibition of GluR5 kainate receptor-mediated synaptic currents in the basolateral amygdala, indicating that it may protect against seizures, at least in part, through suppression of GluR5 kainate receptor responses.

KEYWORDS: amygdala; GluR5 kainate receptor; AMPA receptor; epilepsy; ATPA; LY293558; topiramate; synaptic transmission; synaptic plasticity

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INTRODUCTION

The amygdala is of special interest in relation to mechanisms of epilepsy because it is part of the medial temporal structures that are often involved in human complex partial seizures.[1] In addition, the amygdala is a key site for kindling in animals.[2,3] Through its connections with the entorhinal cortex and hippocampus, the amygdala plays a pivotal role in the generation and spread of limbic seizure activity. However, the cellular mechanisms that underlie the epileptic susceptibility of the amygdala are only beginning to be understood. The circuitry of the amygdala seems to favor synchronized firing of the type that is required for epileptic discharges.[4] Additionally, activity-dependent synaptic plasticity mechanisms (possibly triggered during kindling) likely play a role in modifying the efficacy of certain amygdala synapses, leading to a bias towards paroxysmal epileptic activity.[5] A diversity of neurotransmitter mechanisms undoubtedly participate in amygdala epileptogenenesis. On the basis of studies in the *in vitro* amygdala slice, we have developed evidence that GluR5 kainate receptors, a type of ionotropic glutamate receptor, plays a unique role in triggering seizure discharges. Our studies have focused on the basolateral amygdala (BLA), which is an amygdala nucleus that is highly susceptible to epileptogenesis.[6,7] Here we review recent experiments addressing the anatomical localization and functional roles of GluR5 kainate receptors in the BLA. These studies demonstrate that GluR5 kainate receptors participate in synaptic transmission and synaptic plasticity in the BLA. In addition, we found that selective activation of amygdala GluR5 kainate receptors elicits synchronized bursting of BLA neurons *in vitro* and limbic seizure activity in the intact animal. Overall, our observations implicate GluR5 kainate receptors as a substrate for amygdala epileptic activity.

KAINATE AND AMYGDALA EPILEPTOGENESIS

Kainate, a neuroexcitant and excitotoxin derived from the marine algae *Digenea simplex*, is an agonist of some ionotropic glutamate receptors and is well recognized as a proconvulsant substance.[8] Although other glutamate receptor agonists can induce intense convulsive seizures when administered to animals, kainate is unique among the common agonists (e.g., NMDA, AMPA) in that low systemic doses produce prolonged limbic seizures (wet-dog shakes, facial and forelimb clonus, and rearing).[9] A high proportion of animals surviving such an attack of limbic status epilepticus go on to have spontaneous seizures throughout their lives.[10] Thus, in addition to its proconvulsant ("seizure-inducing") properties, kainate is epileptogenic in that it can induce a long-lasting transformation to a seizure-susceptible state. The seizures occurring in kainate-kindled animals are of the limbic type, suggesting involvement of temporal lobe structures including the amygdala. Moreover, it is well recognized that amygdala neurons are particularly sensitive to excitotoxic damage by kainate.[11,12] Therefore, the amygdala is a likely target site for the pro-epileptic action of kainate. In fact, prolonged limbic status epilepticus is produced by focal intra-amygdaloid infusion of kainate.[13] After a variable latent period of 2 weeks or more in which the animals exhibit interictal discharges but no behavioral seizures, spontaneous limbic and secondarily generalized seizures may occur.[14] Therefore, kainate-induced activation of the amygdala region alone is sufficient for limbic epileptogenesis.

KAINATE RECEPTORS

Fast excitatory neurotransmission in the mammalian central nervous system is mainly mediated by glutamate acting on NMDA, AMPA, and kainate ionotropic glutamate receptors. These receptors are multi-subunit (probably tetrameric) membrane proteins that act as cation channels.[15] In response to synaptically released glutamate, they permit sodium (and in some cases also calcium) to enter into the neuron, generating depolarization and excitation. Recently, we demonstrated through the use of selective pharmacological antagonists[16] that kainate receptors play a role in excitatory neurotransmission in the amygdala.[17] The subunit proteins that constitute kainate receptors are termed GluR5, GluR6, GluR7, KA1, and KA2 (more recent IUPHAR nomenclature GLU_{K5}–GLU_{K7}, GLU_{K1}, and GLU_{K2}). These receptor subunits have molecular masses of ~100 kDa (approximately 900 amino acids) and, based upon their amino acid sequences, are ~40% homologous to AMPA receptors and ~20% homologous to NMDA receptors.

Although there is only limited information on the molecular diversity of kainate receptors in brain neurons, there are a number of ways such diversity could be generated. GluR5-7 and KA1-2 subunits can combine in various stoichiometries to form functionally distinct heteromeric kainate receptor subtypes. (KA1 and KA2 do not form functional channels by themselves.) In addition, individual subunits can exist in alternatively spliced forms. GluR5 and GluR6 kainate receptors are susceptible to structural modification through mRNA editing, as occurs for the GluR2 AMPA receptor subunit. The subunit pre-mRNA is believed to undergo posttranscriptional revision at specific sites so that it encodes a different amino acid at these sites from the one coded by the gene. A particularly critical site for such editing is the glutamine/arginine (Q/R) site in the M2 segment, which regulates the permeability properties of the receptor. In the case of homomeric GluR6 receptors, the Q-to-R substitution decreases the permeability to calcium and transforms the rectification properties from inwardly rectifying to linear or slightly outwardly rectifying. Similarly, heteromeric receptors containing an edited GluR5 or GluR6 subunit are calcium-impermeable and linear or outwardly rectifying. Therefore, calcium-permeable kainate receptors exclusively contain unedited GluR5 or GluR6 subunits.

MODERN PHARMACOLOGY OF KAINATE RECEPTORS

Many kainate receptor agonists, including the natural agonist glutamate, nonselectively activate AMPA receptors as well as kainate receptors. Kainate, the prototypic agonist for kainate receptors, induces kainate receptor currents that desensitize over the course of several hundred milliseconds, even in the continued presence of the agonist.[18] However, kainate also activates AMPA receptors at similar concentrations (EC_{50} ~150 μM), eliciting currents that do not desensitize.[19] Thus, kainate cannot be used to selectively activate kainate receptors. Domoic acid, found naturally in marine phytoplankton diatoms such as *Pseudo-nitzschia multiseries* (a cause of shellfish poisoning), is approximately 10-fold more potent than kainic acid as an agonist of kainate receptors.[20] However, like kainate, it activates AMPA receptors.[19]

Newer pharmacological tools permit the roles of kainate receptors to be characterized without confounding effects of AMPA receptor activation. For example, several AMPA/kainate agonists have been identified that preferentially activate kainate receptors containing the GluR5 subunit. One such agonist is ATPA, a *tert*-butyl analog of AMPA.[21] ATPA is a potent agonist of recombinant homomeric and heteromeric GluR5 kainate receptors (EC_{50} values, 0.6–2 μM),[22,23] but a weak, partial agonist at AMPA receptors and GluR6/KA2 kainate receptors.[24,25] Therefore agonists such as ATPA permit GluR5 kainate receptors to be selectively activated. 2,3-Benzodiazepine non-NMDA antagonists including GYKI 53655 and GYKI 52466 are an additional set of tools that have been critical in the study of kainate receptors.[26] These noncompetitive (allosteric) antagonists preferentially block AMPA receptors and not kainate receptors, with a selectivity of >10- to 200-fold.[18,27] Thus, at appropriate concentrations, these drugs largely eliminate AMPA receptor-mediated responses, allowing kainate responses to be studied in isolation. Decahydroisoquinolines, such as LY293558, LY296486, and LY382884, make it possible to confirm that a response obtained in the presence of AMPA receptor blockade is mediated specifically by GluR5 kainate receptors.[21,28–30] These compounds have varying degrees of AMPA receptor blocking activity and also were recently demonstrated to inhibit homomeric or heteromeric kainate receptors containing at least one GluR5 subunit. They have no detectable activity at homomeric GluR6 kainate receptors.

GLUR5 KAINATE RECEPTORS MEDIATE EXCITATORY SYNAPTIC TRANSMISSION IN THE AMYGDALA

In situ hybridization studies have demonstrated that the various kainate receptor subunit mRNAs are widely expressed within the nervous system in a nonuniform distribution.[31] The mRNAs have been found in neocortex, limbic system, and cerebellum. Recently, we noted that GluR5 mRNA is strongly expressed in temporal lobe structures, including the amygdala and piriform cortex.[32] These kainate receptors have a variety of roles in synaptic transmission. At some synapses, kainate receptors mediate a portion of the glutamatergic postsynaptic response, whereas at other synapses, kainate receptors act as presynaptic modulators of synaptic release. (For reviews, see Refs. 33 and 34.) In the BLA, the bulk of the glutamatergic excitatory postsynaptic response is mediated by AMPA receptors. However, using selective pharmacological antagonists, we found that GluR5 kainate receptors are responsible for a component (about 30%) of the fast synaptic depolarization ("excitatory postsynaptic potential" or EPSP).[17,32] The GluR5 kainate receptor component, isolated in the presence of the selective AMPA receptor antagonist GYKI 52466 and recorded under voltage-clamp conditions, is shown in FIGURE 1A,B. (The recording solution also contained antagonists of NMDA, $GABA_A$, and $GABA_B$ receptors.) Note that very low concentrations of LY293558 can completely eliminate the kainate receptor-mediated synaptic current; these low concentrations do not substantially affect pure AMPA receptor-mediated synaptic currents. Interestingly, the GluR5 kainate receptor synaptic current has inwardly rectifying properties that are apparent from the current-voltage relationship (not shown). This suggests that at least some of the multimeric GluR5 kainate receptors exclusively contain GluR5 subunits that

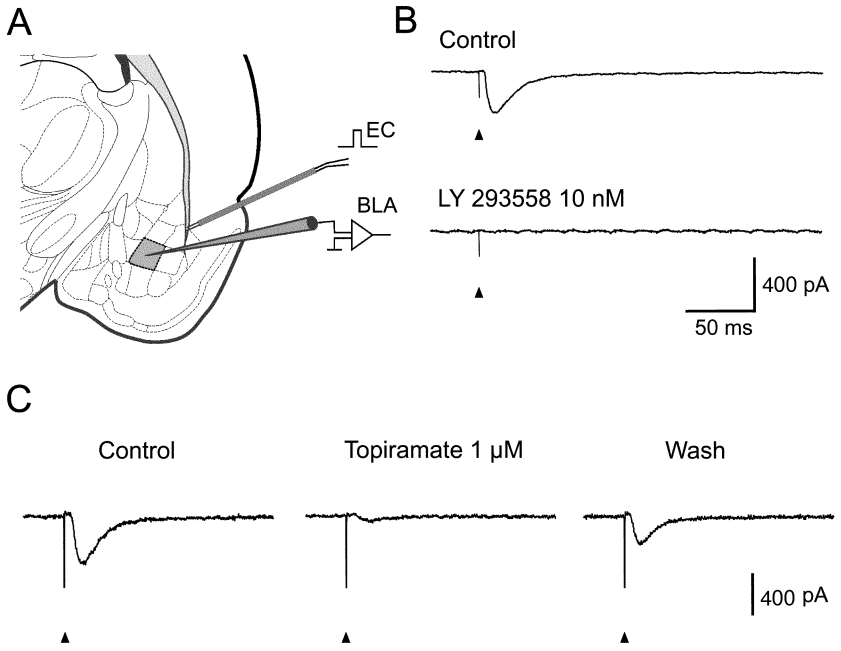

FIGURE 1. GluR5 kainate receptor-mediated excitatory synaptic transmission in the basolateral amygdala (BLA): block by the anticonvulsant topiramate. **(A)** Schematic illustration of the configuration for whole-cell voltage-clamp recording in the rat amygdala slice (coronal section). A tungsten bipolar stimulating electrode placed on the external capsule (EC) is used to deliver 100 µs-duration monophasic stimuli. Patch recordings are obtained from visually identified principal neurons in the BLA. GluR5 kainate receptor responses are isolated by perfusion with 100 µM D-AP5, 50 µM GKYI 52466, 10 µM bicuculline methiodide, and 10 µM SCH 50911 to block NMDA, AMPA, $GABA_A$, and $GABA_B$ receptors, respectively. **(B)** Control trace is the GluR5 kainate receptor-mediated component of EC-evoked synaptic current. The response is rapidly eliminated by addition of 10 nM LY293558, which at these low concentrations selectively blocks GluR5 kainate receptors. Holding potential, –120 mV. **(C)** Topiramate causes a slow block of GluR5 kainate receptor-mediated synaptic current. Fifty-two minutes after onset of perfusion with 1 µM topiramate, the current is largely eliminated (*middle trace*). *Right trace* shows partial recovery 12 minutes after removal of topiramate from the perfusion solution. Holding potential, –70 mV.

are unedited at the Q/R site. In fact, we found that a proportion of GluR5 kainate receptor mRNAs in the BLA are unedited.[32] Such inwardly rectifying GluR5 kainate receptors are expected to be calcium permeable. This property of BLA GluR5 kainate receptors could indicate a role in forms of synaptic plasticity, as is the case for some other calcium-permeable ionotropic receptors such as NMDA and calcium-permeable AMPA receptors.[35]

ACTIVATION OF GLUR5 KAINATE RECEPTORS INDUCES EPILEPTIFORM DISCHARGES

It is well recognized that low concentrations of kainate (1 μM) can induce spontaneous epileptiform activity in *in vitro* brain slice preparations of hippocampus and neocortex.[36–38] However, whether the proconvulsant activity of kainate occurs through activation of kainate or AMPA receptors is uncertain. We used ATPA in an *in vitro* amygdala slice preparation to address the relative roles of kainate and AMPA receptor activation in the induction of epileptiform activity in the amygdala. We found that bath application of ATPA elicited spontaneous synchronized bursting in the BLA within 5–10 minutes of the onset of drug perfusion. The threshold concentration was 2.5 μM, and robust responses were observed at 10 μM (FIG. 2). By contrast, AMPA at comparable concentrations usually led to termination of all activity, presumably because of depolarization inactivation. Similarly, in the BLA, kainate also generally led to termination of activity, which can be attributed to its AMPA receptor agonist activity. Coadministration of the decahydroisoquinoline GluR5 kainate receptor antagonist LY293558 at concentrations of 100–250 nM reduced the frequency of ATPA-induced bursting and terminated bursting at 500 nM. Taken together, these results demonstrate that activation of GluR5 kainate receptors can induce epileptiform discharges. The results also suggest that the *in vitro* pro-epileptic activity of kainate may relate to effects specifically on kainate receptors and not AMPA receptors.

GLUR5 KAINATE RECEPTORS AS TARGETS FOR ANTIEPILEPTIC DRUGS

Ionotropic glutamate receptor antagonists are effective in protecting against various types of seizures in animal models. As a consequence, there has been considerable interest in their potential use in epilepsy therapy.[39,40] However, attempts to develop NMDA receptor antagonists for epilepsy therapy have not been encouraging, and to date, only preliminary clinical trials have been carried out with AMPA receptor antagonists. Inasmuch as selective activation of kainate receptors elicits epileptiform activity (at least in the BLA), it is conceivable that blockade of kainate receptors could suppress seizure activity. In this case, kainate receptors may represent a promising anticonvulsant drug target.

No currently marketed anticonvulsant is believed to interact directly with ionotropic glutamate receptors, with the possible exception of topiramate, which has been reported to block kainate-activated currents in cultured hippocampal neurons.[41] In these prior studies, the specific receptor type targeted by kainate was not established. We found that topiramate, at low concentrations, selectively inhibits GluR5 kainate receptor-mediated synaptic currents in the BLA, but is much less effective against AMPA receptor responses (FIG. 1C). Topiramate block of GluR5 kainate receptor responses was slow, suggesting that it could act indirectly, perhaps affecting second-messenger mechanisms that modulate the activity of kainate receptors. In fact, studies with recombinant kainate receptors in a heterologous expression system have confirmed that the drug does not directly affect the GluR5 kainate receptor channel complex.[42] Evidence indicates that topiramate may modify the phos-

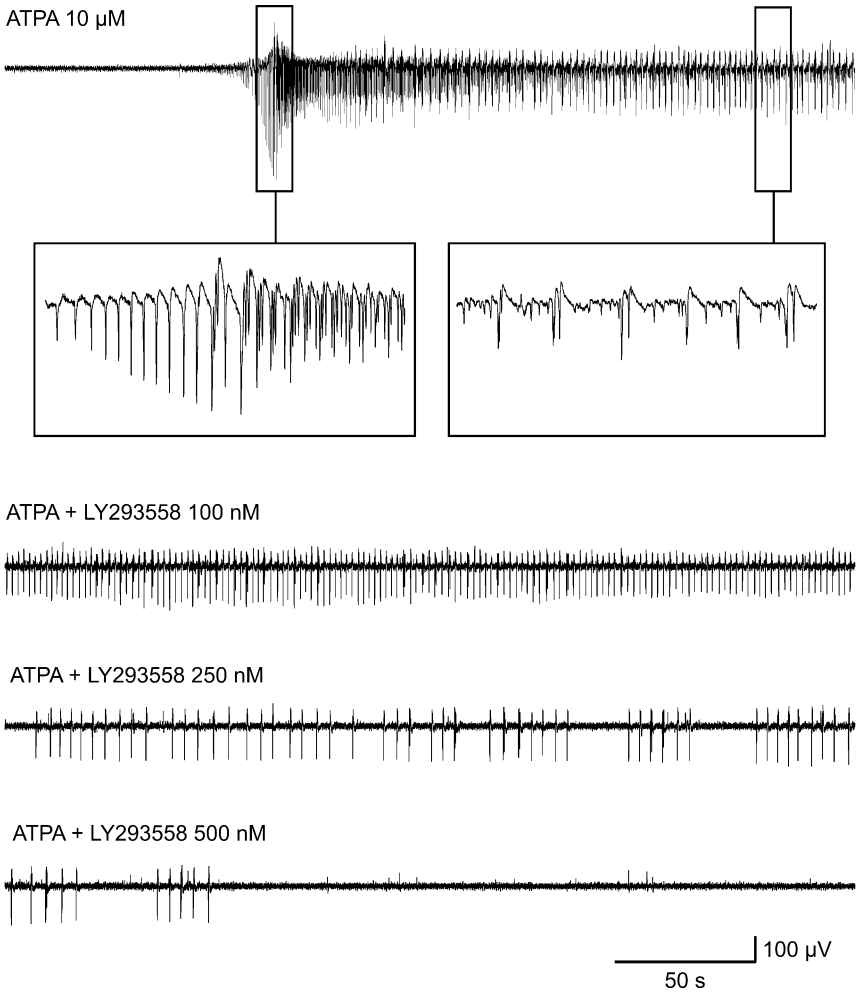

FIGURE 2. Epileptiform activity induced by the GluR5 kainate receptor agonist ATPA in the rat amygdala slice and its block by the GluR5 antagonist LY293558. Extracellular recordings were made from the basolateral amygdala (BLA) in a rat amygdala slice at 31°C. Bath perfusion with 10 µM ATPA elicits spontaneous epileptiform bursts within 10 minutes of the onset of drug application (*top*). Co-perfusion with increasing concentrations of LY293558 results in a reduction in the frequency of bursting and, at 500 nM, cessation of activity. *Boxed areas* in the *top trace* are shown on an expanded time scale in the two insets.

phorylation state of proteins.[43] It will be of interest to determine if this action contributes to its effects on kainate receptors. In any case, the demonstration that topiramate, a highly effective, broad spectrum, antiepileptic agent, can block kainate receptors at low concentrations supports the concept that kainate receptors may represent a promising target for antiepileptic drug development.

ROLE OF KAINATE RECEPTORS IN SYNAPTIC PLASTICITY

The strength of synaptic transmission at amygdala synapses can be modified in an activity-dependent fashion, a phenomenon generally referred to as "synaptic plasticity." Various forms of synaptic plasticity have been described in the amygdala. Some are associated with brief changes in synaptic efficacy, whereas others are enduring. Long-term potentiation (LTP), the prototypical form of enduring synaptic facilitation in the mammalian brain, which has been extensively studied in the hippocampus and neocortex, also occurs in the amygdala,[44–46] where it is believed to play a role in fear conditioning.[47] LTP in the amygdala is typically elicited by a brief high-frequency tetanus. As in other brain regions, LTP in the amygdala is synapse specific and is often dependent on calcium entry through NMDA receptors,[48] but it has also been linked to entry of calcium through voltage-gated calcium channels.[49]

Recently, we reported that low frequency stimulation (LFS) of excitatory afferents to BLA neurons can induce a novel form of enduring synaptic facilitation[50] that, like conventional LTP, requires calcium entry.[32] However, LFS-induced enduring synaptic facilitation has many characteristics that are distinct from LTP. Importantly, this novel form of synaptic facilitation is not dependent on NMDA receptors, but instead requires activation of GluR5 kainate receptors. Thus, decahydroisoquinoline GluR5 kainate receptor antagonists, but not NMDA receptor antagonists, prevent the induction of LFS-induced synaptic facilitation in the BLA. In addition, direct activation of GluR5 kainate receptors with ATPA can cause a robust and long-lasting enhancement in the synaptic response reminiscent of the effects of stimulation. LFS-induced synaptic facilitation develops slowly (over the course of ~15 minutes) in contrast to conventional LTP in which the potentiated response is seen immediately after termination of the stimulation. This suggests that LFS-induced synaptic facilitation may have a distinct mechanistic basis. It is now well recognized that conventional LTP is triggered by postsynaptic receptor activation and may be expressed postsynaptically through an increase in the number of AMPA receptors that contribute to the response. By contrast, whereas LFS-induced synaptic facilitation also appears to be induced postsynaptically, it could be expressed presynaptically through enhanced glutamate release. Another critical difference is that LFS-induced synaptic facilitation is not synapse specific. Inputs onto the target cell other than the pathway stimulated may be facilitated. Such nonspecific enhancement of excitatory inputs could conceivably be a mechanism whereby activation of GluR5 kainate receptors leads to the progressive spread of enhanced excitability, resulting in the conversion to an epileptic state.

ROLE OF KAINATE RECEPTORS IN EPILEPTOGENESIS

Using the selective AMPA receptor antagonist GKYI 52246 and the mixed AMPA/GluR5 antagonist LY293558, we examined whether conventional amygdaloid kindling in the mouse (daily stimulation with a single 1-s duration 60-Hz train) requires activation of GluR5 kainate receptors. Our experiments demonstrate that GluR5 kainate receptor activation is not obligatory for this type of kindling.[51] AMPA/kainate receptor blockers do protect against the expression of amygdala-kindled seizures; however, such antagonists do not appear to slow the rate at which kin-

dling is induced. Rather, induction of this form of kindling seems to be uniquely sensitive to NMDA receptor blockade. On the other hand, it is conceivable that some forms of amygdala epileptogenesis do result from kainate receptor activation. In preliminary experiments we observed that a single intra-amygdala infusion of the GluR5 kainate receptor agonist ATPA in the rat induces limbic status epilepticus and, in some animals, recurrent spontaneous seizures that occur paroxysmally for months after the infusion.[52]

PERSPECTIVE

The various lines of evidence presented here indicate that GluR5 kainate receptor activation can trigger seizures in the amygdala. Because the amygdala is a key substrate for temporal lobe seizures in humans,[1] drugs that target GluR5 kainate receptors could potentially be of value in the treatment of temporal lobe epilepsy. The distribution of GluR5 is more restricted than is that of GluR6. Therefore, selective GluR5 antagonists would be expected to have less neurological and behavioral toxicity than would nonselective kainate receptor antagonists.

Outside the amygdala, GluR5 is likely to be less important in seizure regulation than GluR6, which has more widespread expression in structures relevant to seizures, including the neocortex and hippocampus.[32] Therefore, mice in which the GluR6 gene is disrupted by homologous recombination have reduced (but not absent) sensitivity to the convulsant effects of systemic (intraperitoneal) kainate.[53] Conversely, mice engineered to be deficient in GluR6 Q/R-site editing and therefore express only calcium-permeable GluR6 receptors have enhanced kainate convulsant sensitivity.[54] GluR5 kainate receptors are unlikely to play a significant role in the convulsant activity of systemic kainate, because mice engineered to express only edited (calcium-impermeable) GluR5 receptors are as sensitive to kainate-induced seizures as are control animals or animals expressing only unedited (calcium-permeable) GluR5 receptor subunits.[55] (Edited GluR5 kainate receptors are expected to have markedly reduced current densities.) Moreover, mice in which the GluR5 kainate receptor was deleted by gene targeting show identical sensitivity to systemic kainate as wild-type animals.[56] Thus, although GluR5 may be of special significance in the amygdala, GluR6 kainate receptors are most relevant to the overall convulsant activity of kainate.

How does activation of kainate receptors result in seizure generation? Depolarization induced by gating of these receptors (by either exogenous agonists or endogenously released glutamate) would be expected to directly excite amygdala neurons. However, this would not explain why kainate receptor agonists are uniquely capable of stimulating synchronized epileptiform discharges. Studies in the hippocampus indicate that kainate receptor activation has a variety of additional actions on inhibitory and excitatory systems that could contribute to seizure induction. For example, it has been shown that activation of kainate receptors can markedly enhance the spontaneous firing of GABAergic interneurons.[33,57] Although this might be expected to increase inhibition, extracellular GABA accumulation could desensitize postsynaptic $GABA_A$ receptors and activate presynaptic $GABA_B$ receptors, ultimately leading to reduced inhibition and the promotion of epileptic activity. Other studies have indicated that activation of kainate receptors on interneurons depresses GABA re-

lease.[21,58] In addition to effects on GABAergic inhibition, in the hippocampus, kainate receptors have complex modulatory effects on glutamate release. In most cases, this effect is inhibitory in nature and mediated through presynaptic mechanisms.[59] However, Contractor *et al*.[60] found that excitatory synaptic currents evoked in CA3 neurons by perforant path stimulation were enhanced by kainate receptor activation. Although it has yet to be determined whether this effect is mediated presynaptically on axon terminals or postsynaptically on dendrites, it failed to occur in slices from animals in which GluR5 or GluR6 had been deleted, indicating involvement of these kainate receptor subunits. Moreover, low concentrations of kainate can depolarize mossy fiber terminals, resulting in enhanced excitatory synaptic transmission onto CA3 pyramidal neurons,[61] and kainate receptors seem to play a role in forms of short-term synaptic facilitation at mossy fiber synapses,[62] although these effects largely occur through presynaptic mechanisms that require GluR6 and not GluR5 receptors. To the extent that such forms of synaptic facilitation are involved in the generation of epileptic activity, kainate receptor agonists with GluR6 activity (e.g., kainate but not ATPA) might act through these mechanisms.

In conclusion, despite the long-standing recognition of kainate receptors as a unique type of ionotropic glutamate receptor, the roles of these receptors in seizure generation and epileptogenesis are only now being defined, and the relative contributions of specific kainate receptor subtypes is still controversial. Kainate receptors containing the GluR6 subunit are undoubtedly important, given their widespread distribution and unique role in seizures induced by systemic kainate. Nevertheless, GluR5 appears to be of significance in the amygdala, a critical brain region for temporal lobe epilepsy. In the future, it is expected that kainate receptors will attract increasing attention as potential targets for the development of epilepsy drug treatments.

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